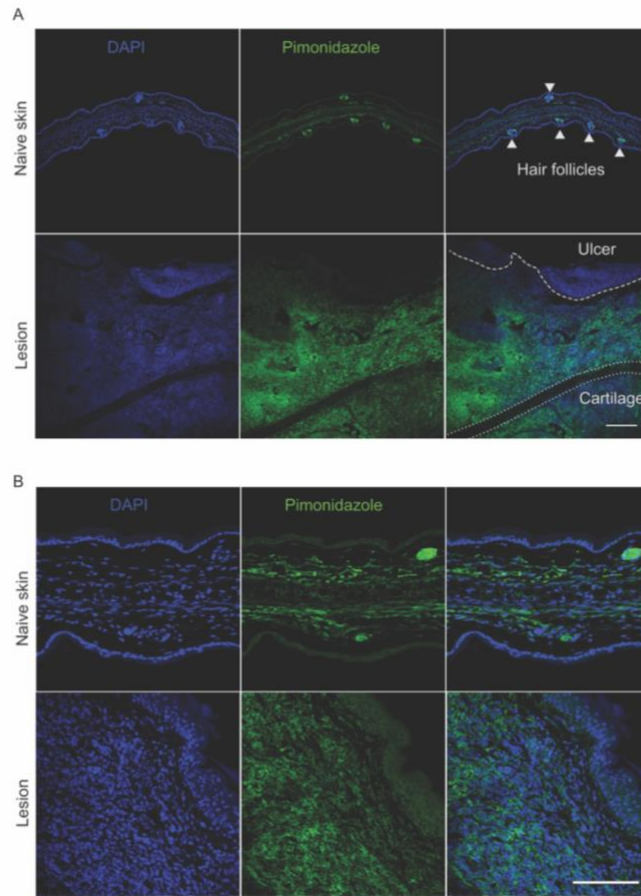


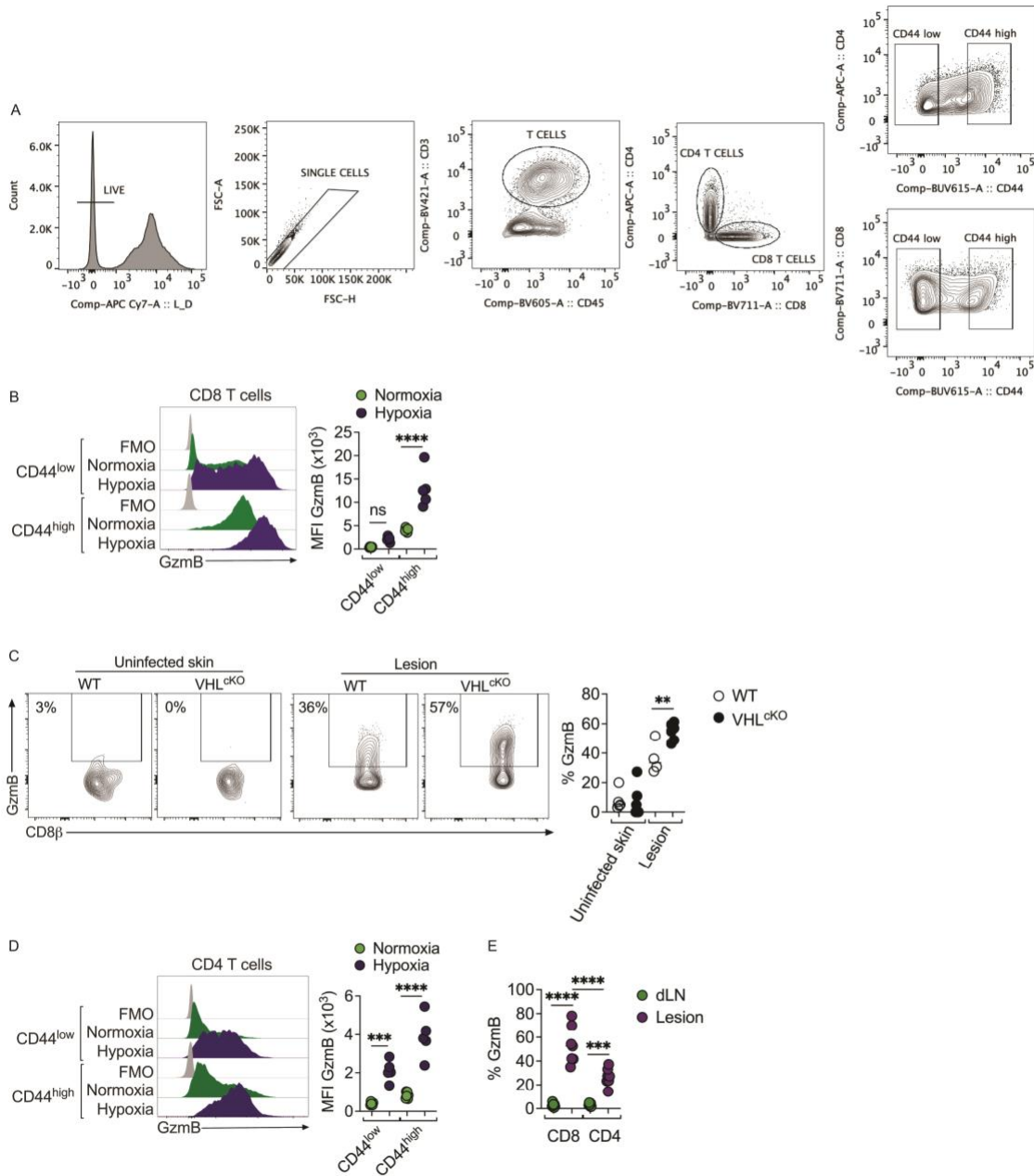
Supplemental Figure 1. Differences between CD8 T cells in lesions and dLNs.

(A) IFN- γ expression in CD8 T cells from dLNs and lesions from C57BL/6 mice in week two post-infection with *L. major*. Representative data from more than three experiments with at least four mice per experiment. (B) Frequency of T cells in lesions from *L. major* infected C57BL/6 mice treated with FTY720 or vehicle daily 12 days post-infection for 10 days. Data representative from two independent experiments with five mice per group. (C-D) C57BL/6 mice were infected with *L. major*, and at the peak of the lesion, antigen-experienced (CD44^{high}) CD8 T cells were purified by flow cytometry cell sorting and used for RNA-seq. Heat map of top 20 differentially expressed genes overexpressed in CD8 T cells (C) from lesions compared to dLN, and (D) from dLN compared to lesions. **** $P \leq 0.0001$, by 2-tailed Student's *t*-test (A and B).



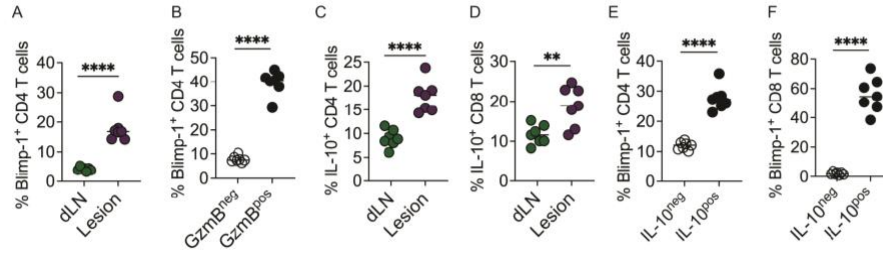
Supplemental Figure 2. Pimonidazole expression in *Leishmania*-infected skin.

C57BL/6 mice infected with *L. major* received pimonidazole one hour before euthanasia at two weeks. **(A)** Individual images from confocal microscopy (Figure 2A). Nuclear (DAPI) staining (blue) and pimonidazole (green) in contralateral ears (naïve skin) and infected ears (lesions) for two weeks. Scale bar = 200 μm. **(B)** Individual images from confocal microscopy (Figure 2B). Nuclear (DAPI) staining (blue) and pimonidazole (green) in contralateral ears (naïve skin) and infected ears (lesions) for two weeks. Scale bar = 100 μm.



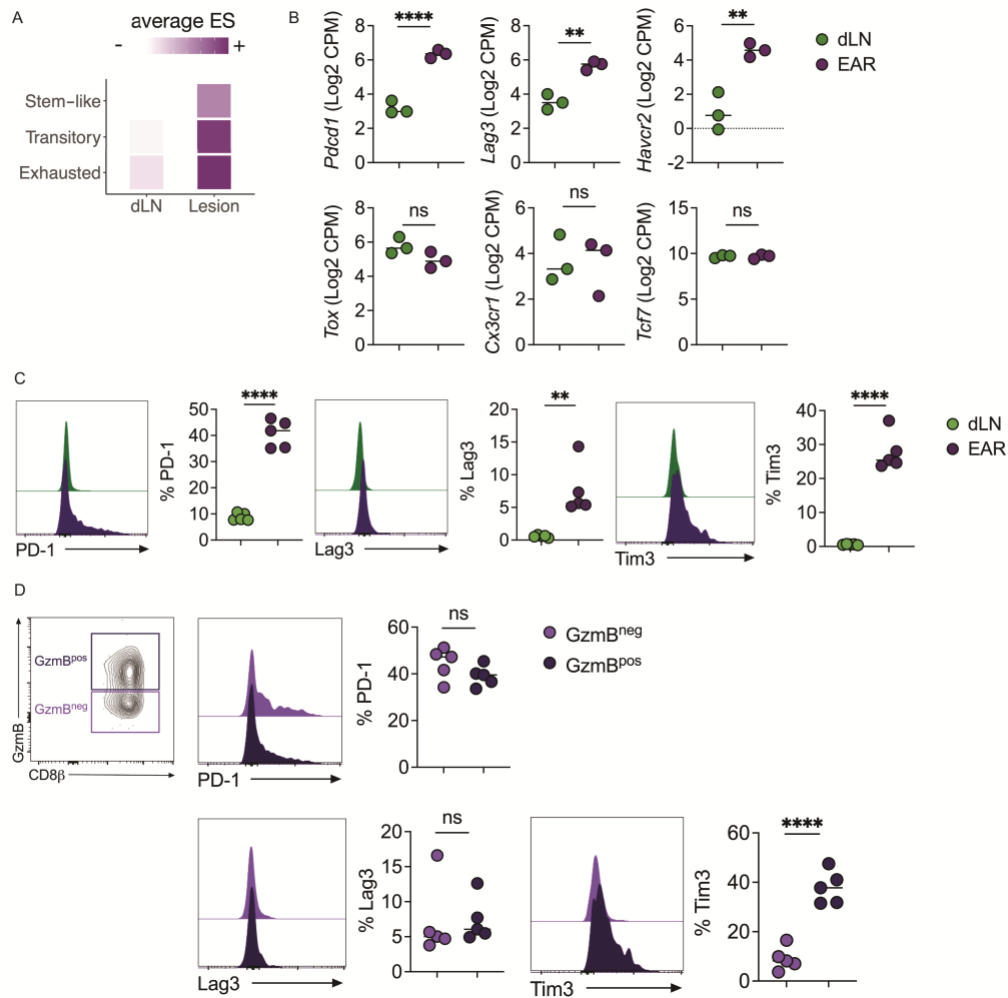
Supplemental Figure 3. Hypoxia induces GzmB expression in CD8 and CD4 T cells.

(A) Gating strategy for experiments in Figure 2D-F and Supplemental Figure 3B and D. (B) Granzyme B (GzmB) expression in naïve (CD44^{low}) or antigen-experienced (CD44^{high}) CD8 T cells from dLNs of C57BL/6 mice infected with *L. major* stimulated with anti-CD3 and anti-CD28 and cultured under normoxia (21% O₂) or hypoxia (1% O₂). (C) GzmB frequency in CD8 T cells in lesions of WT or VHL^{ckO} mice infected with *L. major* for two weeks. (D) GzmB expression in naïve (CD44^{low}) or antigen-experienced (CD44^{high}) CD4 T cells from dLNs of C57BL/6 mice infected with *L. major* stimulated with anti-CD3 and anti-CD28 and cultured under normoxia (21% O₂) or hypoxia (1% O₂). (E) GzmB expression in CD4 T cells from dLNs and lesions from C57BL/6 mice in week two post-infection with *L. major*. (A, B, and D) Representative data from more than three experiments with at least four mice per experiment. (C) Data from two independent experiments combined. (E) Representative data from three experiments with at least five mice per experiment. **P ≤ 0.01 , ***P ≤ 0.001 and ****P ≤ 0.0001 , by one-way ANOVA. ns = non-significant FMO = Fluorescence Minus One.



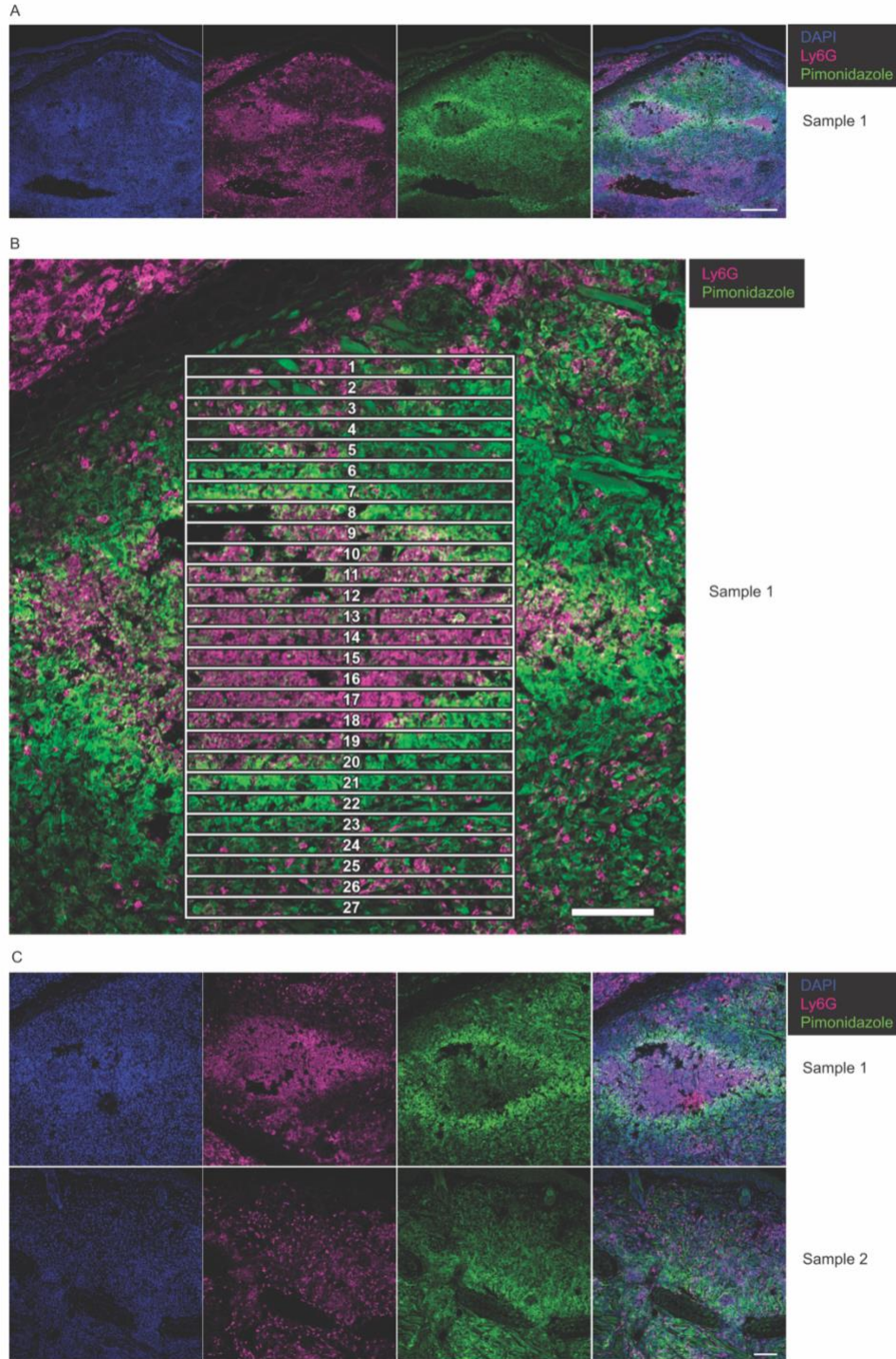
Supplemental Figure 4. The impact of Blimp-1 expression in CD4 and CD8 T cells.

Blimp-1 YFP reporter mice were infected with *L. major* for one week. **(A)** Blimp-1 YFP reporter mice expression in CD4 T cells from dLNs and lesions. **(B)** Blimp-1 YFP expression in Granzyme B (GzmB)^{pos} or GzmB^{neg} CD4 T cells. **(C-D)** IL-10 expression in **(C)** CD4 and **(D)** CD8 T cells from dLNs and lesions. **(E-F)** Blimp-1 YFP expression in IL-10^{pos} or IL-10^{neg} **(E)** CD4 T cells and **(F)** CD8 T cells. Representative data from three independent experiments with 3-8 mice per experiment. ***P* ≤ 0.01, and ****P* ≤ 0.001, by 2-tailed Student's *t*-test (**A**, **C**, and **D**) and paired *t*-test (**B**, **E**, and **F**). ns = non-significant.



Supplemental Figure 5. CD8 T cells from lesions express markers of terminal exhaustion.

C57BL/6 mice were infected with *L. major*, and at the peak of the lesion, antigen-experienced (CD44^{high}) CD8 T cells were purified by flow cytometry cell sorting and used for RNA-seq. **(A)** Enrichment score (ES) of ‘Stem-like,’ ‘Transitory,’ and ‘Exhausted’ (states-of-exhaustion) gene expression signatures in CD8 T cells. **(B)** Gene expression of exhaustion markers in CD8 T cells from dLN and lesions. **(C)** PD-1, Lag3, and Tim3 expression in CD8 T cells from dLNs and lesions from C57BL/6 mice in week two post-infection with *L. major*. **(D)** PD-1, Lag3, and Tim3 expression in granzyme B (GzmB) positive and negative CD8 T cells from lesions. **(C-D)** Representative data from two experiments with five mice per experiment. ** $P \leq 0.01$, and **** $P \leq 0.0001$, by 2-tailed Student’s *t*-test **(B-D)**. ns = non-significant.



Supplemental Figure 6. Neutrophil and pimonidazole expression in *Leishmania*-infected skin.

C57BL/6 mice infected with *L. major* received pimonidazole one hour before euthanasia at two weeks. **(A)** Individual images from confocal microscopy (Figure 5C). Nuclear (DAPI) staining (blue), Ly6G (pink), and pimonidazole (green) in the skin infected for two weeks. Scale bar = 200 μm . **(B)** The confocal microscopy image was divided into 27 regions to measure the pixel intensity of Pimonidazole (green) and Ly6G (pink) shown in Figure 5D. Scale bar = 100 μm . **(C)** Individual images from confocal microscopy (Figure 5E). Nuclear (DAPI) staining (blue), Ly6G (pink), and pimonidazole (green) in the skin infected for two weeks. Scale bar = 100 μm .